REMARKS

Claims 87, 88, and 90-118 are pending in this application. Claims 117 and 118 have been amended to remove the dependency from canceled claim 89. Claims 87, 90, and 91 have been amended to more particularly point out what Applicants regard as the invention. In particular, claims 87 and 91 have been amended to remove "histidine" from the list of substitutions at position 433 of human IgG constant domain. In addition, Applicants note that "lysine" was incorrectly deleted from claim 90 by their April 18, 2005 Amendment. Accordingly, "lysine" has been re-inserted into claim 90 by this Amendment. Support for a "lysine" at position 433 as recited in claim 90 is found *inter alia* in the specification, for example at page 7, lines 8-10. Applicants believe that these amendments are supported by the specification of the present application and do not constitute new matter. Upon entry of this Amendment, claims 87, 88, and 90-118 will be pending and under examination.

1. INTERVIEW SUMMARY

Applicants thank the Examiner and his supervisor, Examiner Chan, for granting an interview with Applicants' attorneys, Margaret Brivanlou and Janet Martineau, and inventor Dr. William F. Dall'Acqua on September 7, 2005 to discuss the outstanding rejections to the claims in the subject application. During the interview, Applicants agreed to provide a Declaration in support of their position that the amino acid substitutions intended by the subject claims, which are identified by their position number according to the EU index as set forth in the reference text Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, 5th ed., 1991 NIH Pub. No. 91-3242 (hereinafter "the Kabat reference"), and not with reference to a particular sequence identified in the claims, are clear to one of skill in the art. Dr. Dall'Acqua explained that the EU index set forth in the Kabat reference was, at the time of filing the subject application, a well known standard numbering system for identifying amino acid residues in the highly conserved constant domains of immunoglobulin molecules. A Declaration by Dr. Dall'Acqua is submitted with this Amendment.

2. FORMALITIES

The Examiner stated that claims 117 and 118 depend from canceled claim 89. In response, Applicants have amended claims 117 and 118 to remove this dependency.

Applicants note that the markup of the claims submitted with their April 18, 2005 Amendment contained certain inaccuracies. Namely, certain insertions were inadvertently not underlined in the markup of claims 87, 88, 90, 91, 102, 107, and 108. A corrected markup of the claims is submitted herewith as **Exhibit A**.

3. THE REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 87, 88 and 90-118 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner asserted that the recitation of amino acid positions in the claims without providing a reference sequence is indefinite and ambiguous because different laboratories may have different numbering of the same protein.

The subject claims are directed to a modified IgG molecule comprising one or more amino acid substitutions at particular amino acid positions in the heavy chain *constant domain*, numbered *according to the EU index as in Kabat* (emphasis added).

In response to the Examiner's rejection, Applicants maintain their position that the reference in the claims to amino acid positions in an IgG heavy chain constant domain ("CH") numbered according to the EU index as in Kabat is clear and definite to one of skill in the art. Specifically, Applicants submit that (1) the Kabat reference was a well-known and widely used reference text in the art at the time of filing the subject application; (2) the EU index was well-established as a standard numbering scheme for the CH region of IgG molecules at the time of filing; (3) given an amino acid position in the CH region of an IgG molecule, numbered according to the EU index as in Kabat, it is a matter of routine skill to determine the corresponding amino acid position in any IgG sequence; and (4) the inclusion of the EU index in the Kabat reference has ensured its continued recognition as a standard numbering scheme for the CH regions of IgG molecules for the foreseeable future.

In support of their position, Applicants submit herewith, as **Exhibit B** (including **Exhibits 1-9**), a Declaration by Dr. William F. Dall'Acqua. The Declaration describes the unique structural features of IgG molecules that enabled the development of a standard numbering scheme, *i.e.*, the EU index, for the CH region of these molecules. This standardization was possible because the CH region, which comprises three domains designated CH1, CH2, and CH3, is highly conserved in terms of overall structure.

Importantly, the amino acid sequence structure of the CH region is practically invariant among antibodies of the same isotype, such as IgG antibodies. Thus, a single numbering scheme such as the EU index can be used to number any CH region of an IgG molecule. Dall'Acqua Declaration ¶ 6 (hereinafter "Declaration").

The EU index is an art-recognized standard numbering scheme for numbering the CH region of IgG molecules. The EU index is based on the sequence of the "Eu" protein, published in 1969, which was the first IgG molecule to be completely sequenced. The numbering of the Eu protein sequence was adopted as the reference standard against which other IgG molecules were compared. As early as 1991, the EU index was so established in the art that it was included alongside the "Kabat numbering" scheme in the tables of CH region immunoglobulin sequences set forth in the Kabat reference. Thus, by the time of the earliest claimed priority of the subject application, December 12, 2000, the EU index was well-established as a standard numbering scheme for the CH region of IgG molecules. The inclusion of the EU index in the Kabat reference has ensured its continued recognition as a standard for numbering immunoglobulin CH regions. Declaration ¶ 7-10.

In addition, the Kabat reference was a well known reference text that was widely used by those of skill in the art at the time of filing the subject application. Although the number of sequenced immunoglobulin molecules has increased substantially since the Kabat reference was published in 1991, and these sequences are now generally published as searchable databases accessible through the internet rather than as printed volumes of tables, the Kabat reference continues to be regarded by those of skill in the art as a useful and important reference text and the EU index remains a standard numbering system for IgG CH regions. Declaration ¶ 5, 11.

Given an amino acid residue numbered according to the EU index as in Kabat, it is a matter of routine skill to determine the corresponding amino acid position in other immunoglobulin molecules using the Kabat tables. In practice, such alignments are routinely carried out using computer programs that are readily available in the art. However, the sequence similarity in the CH region of IgG molecules is so high that it is also possible for one of skill to make an alignment by hand. Thus, a statement that an amino acid position in the CH region of an IgG molecule is "residue number x according to the EU index as in Kabat" has a definite and precise meaning to one of skill in the art. Moreover, the EU index

is so well-established that a reference to "EU numbering" will continue to have a clear and definite meaning to those of skill in the art for the foreseeable future. Declaration ¶ 12-15.

In summary, the "EU index" as published in the Kabat reference was an art-recognized standard for numbering the CH region of IgG molecules at the time of filing and that its widespread use permits researchers to refer to specific amino acid positions without the need to publish entire sequences. Thus, those skilled in the art could readily determine to which amino acid residues in an IgG CH domain the claims refer.

In view of Applicants' previous arguments made in their Amendment filed April 18, 2005, and further in view of the supporting Declaration submitted herewith, Applicants submit that claims 87, 88, and 90-118 satisfy the requirements of 35 U.S.C. §112, second paragraph, and respectfully request that the Examiner withdraw this rejection.

4. THE REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 87, 88, and 90-118 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Specifically, the Examiner stated that the attempt to incorporate subject matter into the application by reference to the Kabat reference was improper because essential material may only be incorporated by reference to a U.S. patent or patent application, and that incorporation by reference would not be effective until correction is made to comply with the requirements of 37 C.F.R. §1.57(b), (c), or (d).

Applicants understand the Examiner's position to be that the Kabat reference is "essential" to the practice of the claimed invention because without the Kabat tables one of skill in the art would not be able to determine which amino acid positions are to be substituted. Applicants further understand the Examiner's reference to compliance with 37 C.F.R. §1.57(b), (c), or (d) was intended to refer to 37 C.F.R. § **1.58** (pertaining to the requirements for chemical and mathematical tables in the specification) because the section cited by the Examiner is not a valid section in the July 1, 2004 update of Title 37, which was the most recent available update of this section at the time the June 1, 2005 Office Action was mailed.

In response, Applicants submit that the Kabat tables are not "essential material" under M.P.E.P § 608.01(p) and therefore incorporation of the tables into the specification is not required. M.P.E.P § 608.01(p) defines essential material as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure, or (3) describe the best mode. In other words, essential material is that which is necessary to satisfy the requirements of 35 U.S.C. §112, first paragraph.

Applicants submit that the tables of the Kabat reference need not be incorporated into the specification to satisfy the requirements of 35 U.S.C. §112 because the Kabat reference was well known in the art at the time of filing the subject application. It is well-settled that Applicants need not provide in their specification that which is already well known in the art. The Federal Circuit has stated that "[a] patent need not teach, and preferably omits, what is well known in the art." *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). In *Hybritech*, the claims at issue were directed to a "sandwich" type immunoassay which requires two high-affinity monoclonal antibodies that bind to the same antigen. *Id.* at 1370. The district court held the patent invalid for lack of enablement because the specification did not teach how to make monoclonal antibodies, how to screen for antibodies that would bind to the antigen, or how to measure antibody affinity for the antigen. The Federal Circuit reversed because methods of making, screening, and measuring the affinity of monoclonal antibodies were known in the art at the time of filing. *Id.* at 1384.

The same issue was recently examined by the Federal Circuit in the context of the written description requirement of 35 U.S.C. §112 in *Capon v. Dudas* (No. 03-1480, Fed. Cir. August 12, 2005). In *Capon*, the inventions were directed to chimeric genes formed from combinations of known DNA segments. The Board of Patent Appeals and Interferences ("the Board") rejected Applicants' claims for lack of written description because the specifications at issue did not include the complete nucleotide sequence of at least one chimeric gene exemplary of the claimed genus. See *Capon* at page 11. The Federal Circuit reversed, explaining that, because the invention does not concern the discovery of gene function or structure, and rather concerns novel chimeric genes prepared from DNA segments of known structure and function, the specification need not recite specific sequences in order to satisfy the written description requirement. *Id.* at page 15. Thus, the Federal Circuit has long held that Applicants need not include in their specification that which was known in the art in

order to satisfy the requirements of 35 U.S.C. §112 (see *e.g.*, *Capon* at page 14)(stating that precedents do not "require a re-description of what was already known").

In support of their position that the Kabat reference was a well-known, widely used reference text for comparing and numbering immunoglobulin sequences, Applicants refer the Examiner to the Declaration by Dr. William F. Dall'Acqua submitted herewith. The Declaration states that the Kabat reference was a well known reference text that was widely used by those of skill in the art of antibody structure at the time of the earliest claimed priority of this application, *i.e.*, as of December 12, 2000, and that it continues to be regarded by those of skill in the art as a useful and important reference text. Declaration ¶ 5.

In view of the remarks above, Applicants submit that claims 87, 88, and 90-118 satisfy the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner withdraw this rejection.

CONCLUSION

Applicants believe that the present claims meet all of the requirements for patentability. Entry and consideration of the foregoing amendments and remarks into the file of the subject application is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

Date: October 3, 2005

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